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Toward the Stereoselective Synthesis of Arthrobotrisin A: Fragment Synthesis and Coupling Studies

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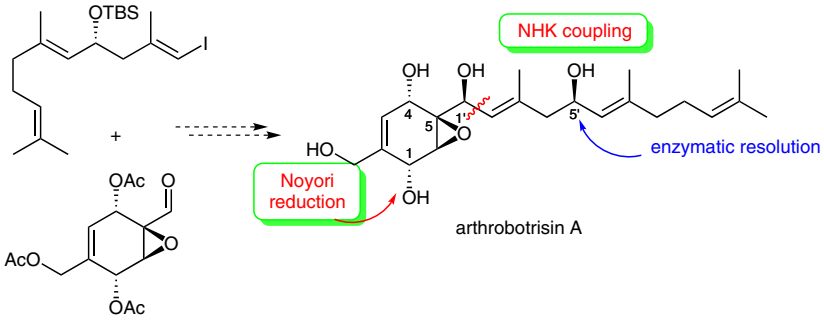


Received: 20.11.2016
Accepted after revision: 20.01.2017
Published online: 24.02.2017
DOI: 10.1055/s-0036-1588950; Art ID: st-2016-b0782-l

Abstract A route towards the stereocontrolled synthesis of arthrobotrisin A based on a Nozaki–Hiyama–Kishi (NHK) coupling strategy was developed. Highlights of the fragment synthesis include enzyme-catalyzed kinetic resolution, Negishi carbometalation–iodination, quinone formation through oxidation with hypervalent iodine, chiral oxazaborolidine-catalyzed asymmetric Diels–Alder reaction with cyclopentadiene, regio- and stereoselective epoxidation, Noyori reduction, retro-Diels–Alder reaction, diastereoselective Luche reduction, and, finally, a Nozaki–Hiyama–Kishi (NHK) coupling of the vinyl iodide fragment.

Key words arthrobotrisin A, Nozaki–Hiyama–Kishi coupling, Diels–Alder reaction, Noyori reduction, Luche reduction, asymmetric synthesis

Among the vast array of terpenoidal natural products, compounds from diverse natural sources that contain an epoxyquinone core are being reported regularly. They have been in the limelight in recent years on account of their structural novelty and their promising wide-ranging biological activities.[1] They can act as antitumor agents[2] or as cytotoxins, and some also inhibit the strand-transfer reaction of HIV-1 integrase.[3] Arthrobotrisins A–C, which belong to this terpenoid family, were isolated from *Arthrobotrys oligospora* by Zhang and co-workers.[4] These compounds exhibit nematocidal and antibacterial properties.[5] The relative configuration of arthrobotrisin A was determined by single-crystal X-ray diffraction and by assignment of its ^{1}H and ^{13}C NMR spectra.[4] Because of their distinctive carbon skeleton and biological activities, the synthesis of the arthrobotrisins attracted our attention. In continuation of our research on the synthesis of new bioactive molecules,[6] we report our studies directed toward a stereocontrolled synthesis of arthrobotrisin A. There are a few literature reports on syntheses of other oligosporons,[7] and some are under investigation in our laboratory (Figure 1).

A retrosynthetic pathway to arthrobotrisin A (**1**) is shown in Scheme 1. We surmised that arthrobotrisin A might be obtainable by a Nozaki–Hiyama–Kishi (NHK) coupling of the vinyl iodide **6** with aldehyde **7**. The substituted

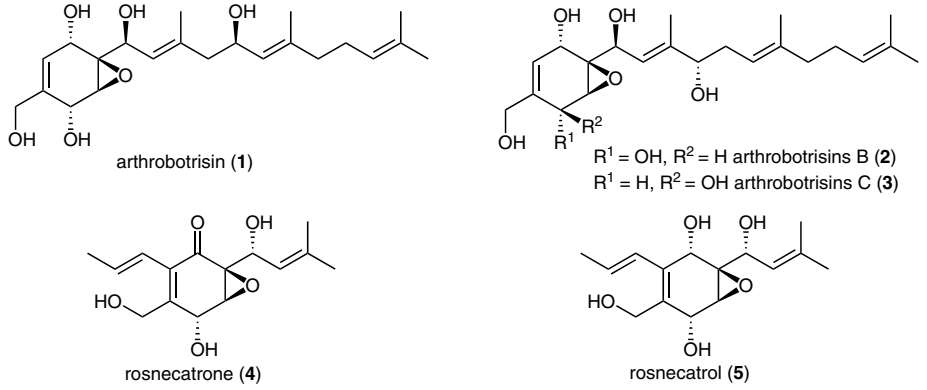
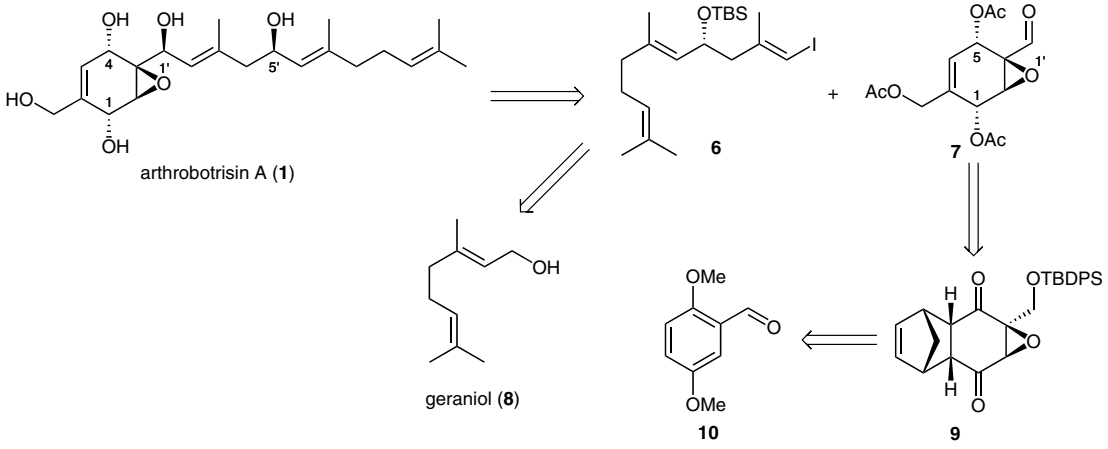


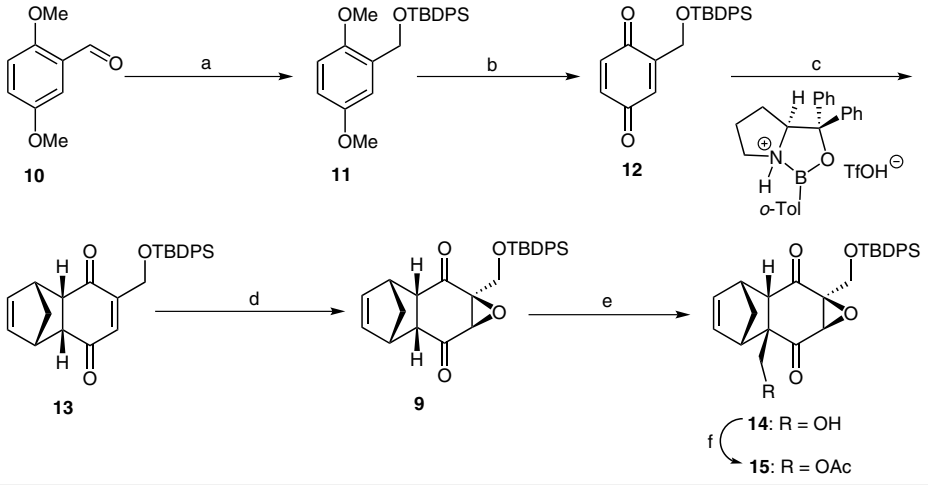
Figure 1 Structures of arthrobotrisins A–C (**1**–**3**) and some other natural products with similar skeletons



Scheme 1 Retrosynthetic analysis for arthrobotrisins A (**1**)

vinyl iodide **6** might be accessible from commercially available geraniol (**8**), and we proposed that the aldehyde **7** might be obtained by a sequential Noyori reduction, retro-Diels–Alder reaction, and Luche reduction of precursor **9**, which should be readily obtainable from easily accessible 2,5-dimethoxybenzaldehyde (**10**).

We began our synthesis of fragment **7** by LAH reduction of 2,5-dimethoxybenzaldehyde (**10**) (Scheme 2). Silylation of the resultant primary alcohol with TBDPSCl gave silyl ether **11** in 97% yield. Oxidation of **11** with an equimolar amount of the trivalent iodine reagent [bis(trifluoroacetoxy)iodo]benzene[8] in 2:1 MeCN–H_2O conveniently gave the *p*-quinone **12** in quantitative yield, whereas the CAN-mediated oxidation[9] gave a poor yield (46%) of the product. The cationic chiral Lewis acid generated from the corresponding oxazaborolidine by protonation with triflic acid was found to be an excellent catalyst for the enantioselective Diels–Alder reaction[10] of *p*-quinone **12** with cyclopentadiene to afford the *endo* Diels–Alder adduct **13** as the major product in 89% yield and 93% ee.[11] This Corey protocol of an enantioselective Diels–Alder reaction catalyzed by a cationic chiral Lewis acid, with a *p*-quinone as the dienophile component and cyclopentadiene as the diene component, resulted in excellent enantioselectivity. Routine functional-group transformations on **13** furnished the (+)-epoxy ketone **9** through regio- and stereoselective epoxidation of the Diels–Alder adduct **13**. The (+)-epoxy ketone **9** was obtained in good yield and with complete *exo*-stereoselectively by using *t*-BuOOH and DBU.[12] This is the most prominent approach to the stereoselective synthesis of epoxyquinone derivatives that have a wide range of biological activities. Monoformylation of **9** with a 35% formalin



Scheme 2 *Reagents and conditions*: (a) $LiAlH_4$, THF, 0 °C, 30 min, 91%; then imidazole, TBDPSCl, CH_2Cl_2, 0 °C to r.t., 3 h, 97%; (b) [bis(trifluoroacetoxy)iodo]benzene, 2:1 MeCN–H_2O, r.t., 30 min, 91%; (c) (*S*)-(–)-*o*-tolyl-CBS-oxazaborolidine, TfOH, cyclopentadiene, CH_2Cl_2, –78 °C, 89% (93% ee). (d) DBU, *t*-BuOOH, CH_2Cl_2, 30 min, 87%; (e) DBU, 35% formalin soln, THF, 0 °C, 30 min, 91% (dr 9:1); (f) Et_3N, Ac_2O, DMAP (cat.), CH_2Cl_2, r.t., 3 h, 95%.

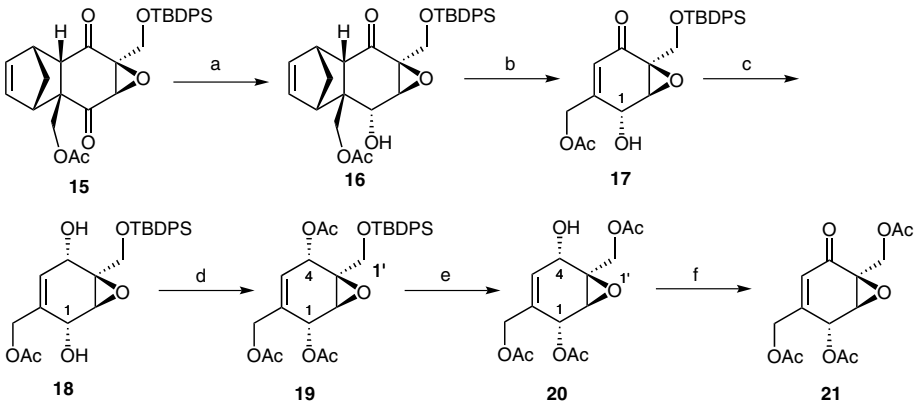
solution in the presence of DBU gave the desired product **14** with high regioselectivity.[7c] The primary alcohol group present in the hydroxymethyl product **14** was protected as its acetate **15** by treatment with triethylamine, Ac_2O, and a catalytic amount of DMAP.

To incorporate the required stereocenter at C1, we initially focused on the stereoselective reduction of **15** with DIBAL-H. Unfortunately, however, the diastereoselectivity of this reduction was poor, resulting in about a 70:30 ratio. Although a variety of methods exist for the stereocontrolled reduction of epoxy ketones, modest diastereoselectivities are often observed.[13] Recently, McIntosh and co-workers described a modification of Noyori's asymmetric catalytic-transfer hydrogenation that is considered to be an attractive alternative procedure for the reduction of epoxy ketones.[14] In the context of our synthesis, the successful implementation of the Noyori reduction on **15** should permit controlled reduction and generation of the appropriate stereocenter at C1 by using Ru(*p*-cymene)[(*S*,*S*)-TsDPEN] (TsDPEN = *N*-tosyl-1,2-diphenylethane-1,2-diamine) as a chiral catalyst (Scheme 3). Indeed, treatment of epoxy ketone **15** with this ruthenium catalyst in CH_2Cl_2 provided the desired allylic alcohol **16**[15] in 81% yield with 20:1 diastereoselectivity. We observed that the stereoselectivity of the reduction of the epoxy ketone **15** was completely under the control of the catalyst.

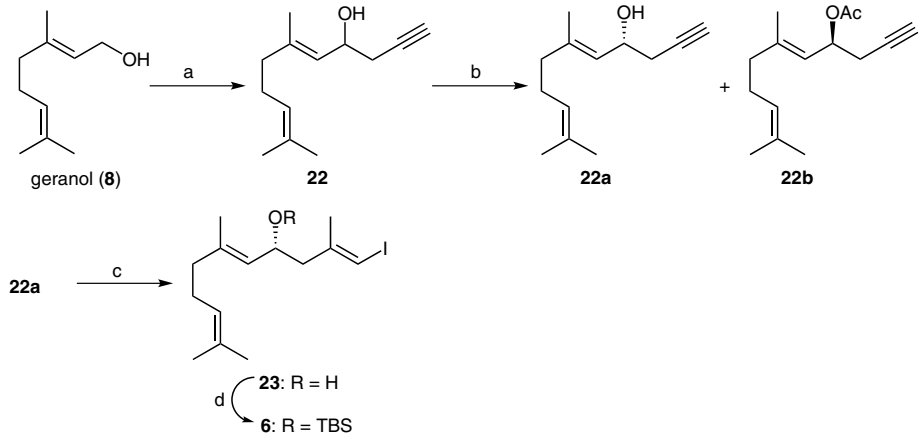
The alcohol **16** was subjected to a retro-Diels–Alder reaction[10] by heating the reaction mixture to 220 °C for two hours in diphenyl ether as solvent, giving enone **17** in 84% yield. The α,β-unsaturated ketone **17** was immediately subjected to a Luche reduction in the presence of $CeCl_3{\cdot}7H_2O$ and $NaBH_4$ at –40 °C to give allylic alcohol **18** in 86% yield and 9:1 diastereoselectivity.[16] In this Luche reduction, hydride ion addition was supposed to take place from the face opposite the TBDPS group, due to steric hindrance. The resulting secondary allylic alcohol groups in **18** were protected as acetate groups in **19** by treatment with Et_3N, Ac_2O, and a catalytic amount of DMAP. During the desilylation of **19** under weakly basic conditions, a migration of the acetyl group from the C4 hydroxy group to the C1′ hydroxy group was observed. We screened various desilylation reagents, such as TBAF and HF-Py, but in all cases, similar results were obtained. The resulting compound **20** was characterized by means of ^1H and ^{13}C NMR spectral analyses. The migration of the acyl group was further confirmed by oxidation of the product **20** with 2-iodooxybenzoic acid (IBX) to give the ketone **21**. This acyl migration is a problem that is often associated with the use of TBAF,[17] and is mainly due to the presence of the C1′ hydroxy group near the *O*-acyl protecting group. This might be overcome by changing the protecting groups in the Luche reduction product **18**; this is under investigation and will be reported in due course. Meanwhile, we wish to report our fragment syntheses and coupling studies.

We began our synthesis of fragment **6** by the oxidation of geraniol (**8**) with IBX in ethyl acetate under reflux conditions to give geranial (Scheme 4). This was treated with freshly prepared propargylmagnesium bromide in dry diethyl ether at –10 °C to give the (±)-homopropargylic alcohol **22**,[18] which was subjected to enzyme-catalyzed resolution.[19] The Amano lipase PS-catalyzed enantiomer-selective acetylation of the racemic alcohol **22** with vinyl acetate gave alcohol **22a** and ester **22b** in good yields and with high enantiomeric excesses (>82%). The absolute configuration of the (–)-homopropargylic alcohol **22a** was assigned by means of a mandelate ester analysis.[20] The enantiopure (*R*)-homopropargylic alcohol **22a** was then subjected to Negishi carbometalation–iodination[21] with Cp_2ZrCl_2, Me_3Al, and iodine to provide the substituted vinyl iodide **23** in 86% yield and with high reaction efficiency and good control of the olefin geometry. The corresponding allylic alcohol **23** was treated with TBSCl and imidazole in CH_2Cl_2 at 0 °C to give silyl ether **6** in 86% yield.

The Nozaki–Hiyama–Kishi (NHK) coupling reaction is a promising protocol for many synthetic strategies.[22] Here, we studied the NHK coupling[23] of vinyl iodide **6** with 3-

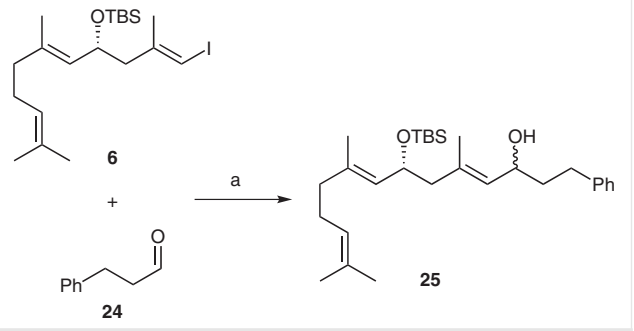


Scheme 3 *Reagents and conditions*: (a) Ru(*p*-cymene)[(*S*,*S*)-TsDPEN], HCO_2H, Et_3N, CH_2Cl_2, 0 °C to r.t., 24 h, 81%; (b) Ph_2O, 220 °C, 2 h, 84%; (c) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, –40 °C, 20 min, 86%; (d) Et_3N, Ac_2O, DMAP (cat.), CH_2Cl_2, 0 °C to r.t., 3 h, 93%; (e) TBAF, THF, 0 °C, 4 h, 84%; (f) IBX, EtOAc, 85 °C, 3 h, 92%.



Scheme 4 *Reagents and conditions*: (a) IBX, EtOAc, 85 °C, 1 h, then HC≡CCH$_2$MgBr (1 M), Et$_2$O, –10 °C, 30 min, 85% (two steps); (b) Amano lipase PS, vinyl acetate, 1:1 hexane–THF, 7 d, 46% of **22a**, 45% of **22b**; (c) Cp$_2$ZrCl$_2$, Me$_3$Al, I$_2$, CH$_2$Cl$_2$, 0 °C to r.t., 14 h, 86%; (d) TBSCl, imidazole, CH$_2$Cl$_2$, 0 °C to r.t., 3 h, 93%.

phenylpropanal (**24**) (Scheme 5). Treating the vinyl iodide **6** and 3-phenylpropanal (**24**) with a large excess of chromium(II) chloride (6 equiv) and a catalytic amount of nickel(II) chloride (0.1 equiv) in dry DMF gave the coupled product **25** in 82% yield and with 65:35 diastereoselectivity. The overall yield for the synthetic fragment **20** was 24.6%, and that of the vinyl iodide fragment **6** was 31.3%.



Scheme 5 NHK coupling of vinyl iodide **6** with 3-phenylpropanal (**24**): (a) CrCl$_2$ (6 equiv), NiCl$_2$ (cat.), DMF, r.t., 24 h, 82% (dr 65:35).

In conclusion, we have synthesized two fragments of arthrobotrisin A, and have studied an NHK coupling of the vinyl iodide fragment **6**. The significance of our synthetic sequence lies in the use of a Negishi carbometalation–iodination, an enzyme-catalyzed resolution, a chiral oxazaborolidine-catalyzed asymmetric Diels–Alder reaction with cyclopentadiene, a hypervalent iodine oxidation to give a quinone, a Noyori reduction, and a regio- and stereoselective epoxidation. The overall yield of synthetic fragment **20** was 24.6%, and that of the vinyl iodide fragment **6** was 31.3%. This is a promising approach for the stereoselective synthesis of epoxyquinone derivatives that have a wide range of biological activities.

Acknowledgment

R.N.K. thanks CSIR, New Delhi, for the award of a fellowship, and Dr. Ahmed Kamal, Outstanding Scientist and Head of the MCP Division, IICT, for his support and encouragement. The authors thank CSIR, New Delhi, for financial support as part of the XII Five Year Plan program under the title ORIGIN (CSC-0108).

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588950.

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